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RICHES, MCKENZIE & HERBERT, LLP SUITE 1800 2 BLOOR STREET EAST TORONTO, ON M4W 3J5 CANADA			EXAMINER KAPUSHOC, STEPHEN THOMAS	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/803,713

Applicant(s)

MARQUESS ET AL.

Examiner

Stephen Kapushoc

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on 29 May 2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,2,7-10,12-18 and 22 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,2,7-10,12-18 and 22 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/S508)
Paper No(s)/Mail Date _____

- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

Claims 1, 2, 7-10, 12-18, and 22 are pending an examined on the merits.

Please Note: The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

This Office Action is in reply to Applicants' correspondence of 5/29/2008.

Applicants' remarks and amendments have been fully and carefully considered but are not found to be sufficient to put the application in condition for allowance. Any new grounds of rejection presented in this Office Action are necessitated by Applicants' amendments. Any rejections or objections not reiterated herein have been withdrawn in light of the amendments to the claims or as discussed in this Office Action.

This Action is made **FINAL**.

Priority

1. The instant application claims priority to Canadian Application 2/422,437 (filed 3/18/2003); it is noted that the Declaration associated with the instant application incorrectly identifies the filing date of Canadian Application 2/422,437 as 3/18/2002.

Acknowledgment is made of applicant's claim for foreign priority based on Canadian Application 2/422,437. It is noted, however, that applicant has not filed a certified copy of the Canadian application as required by 35 U.S.C. 119(b).

Response to Remarks

The amendment to the specification to properly cite the provision application 60/509,755 (fixing the typographical error of 60/509,775) is acknowledged.

Information Disclosure Statement

2. The listing of references in the specification is not a proper information disclosure statement; see for example the citation of references on page 2 of the instant

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specification. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Response to Remarks

Applicants Remarks of 5/29/2008 indicate that an IDS is being obtained and will be submitted. At this time no IDS has been received, and the examiner reiterates that unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Withdrawn Objection Specification

3. The objection to the disclosure for making reference to methods 'using primers having SEQ ID NO: 2 and 3' (see for example page 52), as set forth in the previous Office Action, is **WITHDRAWN** in light of the amendments to the specification.

Oath/Declaration

4. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

It does not identify the foreign application for patent or inventor's certificate on which priority is claimed pursuant to 37 CFR 1.55, and any foreign application

having a filing date before that of the application on which priority is claimed, by specifying the application number, country, day, month and year of its filing.

In the instant case the oath indicates a filing date of Canadian Application 2/422,437 as 3/18/2002, whereas the application appears to be filed 3/18/2003.

Additionally, the Oath/Declaration makes reference to US provisional application 60/509,775 where likely 60/509,755 is intended.

Response to Remarks

Applicants Remarks of 5/29/2008 indicate that a corrected Declaration is being obtained. At this time no corrected Declaration has been received, and the examiner reiterates that Oath is defective.

Withdrawn Claim Objections

5. The objections to claims 1 and 12, as set forth in the previous Office Action, are **WITHDRAWN** in light of the amendments to the claims.

The objection to claims 11 and 19 under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim, as set forth in the previous Office Action, is **WITHDRAWN** in light of the cancellation of claims 11 and 19.

Withdrawn Claim Rejections - 35 USC § 112 2nd - Indefiniteness

6. The following rejections of claims under 35 USC 112 2nd ¶, as set forth in the previous Office Action, are **WITHDRAWN** as detailed below and in light of the cancellation of claims:

The rejection of claims 1-7 as unclear over recitation of the phrases 'amplifying a region of the ob gene polymorphism' and 'the amplified ob gene polymorphism sequences' in claim 1, in light of the amendment to claim 1 to require that the amplified region includes the polymorphic position.

The rejection of claims 1-7 as unclear over recitation of the phrase 'based on the presence of a particular ob gene polymorphism' in claim 1, in light of the amendment to claim 1 to indicate the polymorphism is at 'a specific polymorphic position'.

The rejection of Claims 1-7 as unclear over recitation of the phrase 'selecting the type of livestock animal' in light of the amendment to claim 1 to require bovines.

The rejection of claim 3 as unclear, in light of the cancellation of the claim.

The rejection of claims 12, and 13, 20, 21, and 22 as unclear because while the preamble of the claim states that the claim is drawn to a method of identifying those animals having increased milk productivity, in light of Applicants' arguments and the requirements of claim 12 that the ob genotype is determined 'wherein animals that possess the T-containing allele of the ob gene have increased milk productivity'

The rejection of claims 14, 15, 20, 21, and 22 as unclear because while the preamble of the claim states that the claim is drawn to a method of breeding livestock animals to increase milk production in the offspring, there is no method step in which

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any animal is actually bred or the milk production in any offspring is increased, in light of the amendment to claim 14 to require a step of breeding the bovine animal.

Maintained Claim Rejections - 35 USC § 112 2nd - Indefiniteness

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 2, 8-10, 13, 16-18 and 22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 8-10 are unclear because while the preamble of claim 8 states that the claim is drawn to a method of increasing milk production in a selected group of livestock, there is no method step in which the milk production of any group is actually increased. It is thus unclear how the purpose of the claim, as stated in the preamble, is accomplished by the method steps of the claim.

Response to Remarks

Applicants have traversed the rejection and argued (p.8-9 of Remarks) that 'the method of knowing to select for a T allele will increase the milk production'. The argument is not persuasive. The method as claimed requires only 'selecting animals that possess the T-containing allele for inclusion in the group'. However because simply selecting an animal is not actually creating a group, the claims do not in fact require any group of specific animals. The claims may be made more clear by including

a final process step of, for example, 'creating a group of selected animals, wherein the group of selected animals has an increased milk production'.

The rejection as set forth is **MAINTAINED**.

Claims 16, 17, 18, and 22 are unclear because while the preamble of the claim states that the claim is drawn to a method of increasing milk production in a selected group of livestock animals, there is no method step in milk production of any group is actually increased. It is thus unclear how the purpose of the claim, as stated in the preamble, is accomplished by the method steps of the claim.

Response to Remarks

Applicants have traversed the rejection and argued (p.9 of Remarks) that 'animals harboring at least one T allele will be included in a new sub group - which will have an increased proportion of T alleles; which has been demonstrated to increase milk production'. The argument is not persuasive. The method as claimed requires only 'selecting animals that possess the T-containing allele for inclusion in the group'. However because simply selecting an animal is not actually creating a group, the claims do not in fact require any group of specific animals. The claims may be made more clear by including a process step of, for example, 'creating a group of selected animals, wherein the group of selected animals has an increased milk production'.

The rejection as set forth is **MAINTAINED**.

Claims 2, 10, 13, and 18 are unclear over the recitation of the phrase 'with respect to' in reference to an allele of the ob gene. For example, claim 2 recites 'a TT animal homozygous with respect to the T-allele of the ob gene', where it is unclear if applicant intends to claim an animal with particular nucleotide content at a specific polymorphic position in a particular gene, or some other content at another position in some way related the polymorphic position.

Response to Remarks

Applicants have traversed the rejection and argued (p.9 of Remarks) that 'it is clear that Applicant intends to claim an animal with a particular nucleotide content at a specific polymorphic position in a specific gene, the ob gene'. The argument is not persuasive. The phrase 'with respect to' is not given any limiting definition in the specification, nor is it an art recognized phrase to indicate a specific relationship among nucleic acid sequences or genotypes. The Examiner maintains that the phrase renders unclear the particular nucleotide content requires of the claims methods.

The rejection as set forth is **MAINTAINED**.

New Claim Rejections - 35 USC § 112 2nd – Indefiniteness

9. Claims 8-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 8-10, 16-18 and 22 are unclear over recitation of the phrase "which results from a change from Arginine to Cysteine" with regard to the T-containing allele in

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the ob genotype, as recited in claims 8 and 16. It is unclear how a change in amino acids can result in, or cause, the required nucleic acid allele.

Maintained Claim Rejections - 35 USC § 112 1st - Description

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 1, 2, 7-10, 12-18, and 22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is referred to the Written Description Training Materials revised March 25, 2008, available at www.uspto.gov.

The claims of the instant application are drawn to methods for the identification and selection of animals with particular phenotypes based on the analysis of nucleic acid sequences. The claims are broadly drawn to the detection and selection of animals with the T-allele or the C-allele of the ob gene. While claim 1 requires the amplification of a region of the ob gene with the primer pair of SEQ ID NO: 4 and 5 and hybridization with probes consisting essentially of SEQ ID NO: 6 and 7, because it is unclear how SEQ ID NOs: 4-7 are related to the sequences of the ob gene, and the specification provides no examples of a method for detecting any ob gene

polymorphisms using SEQ ID NOs: 4-7, it is not clear how these sequences address the description of the T-allele or the C-allele of the ob gene.

The specification further provides the sequence of a portion of the ob gene from bovine as SEQ ID NO: 1 and 2, where SEQ ID NO: 1 has a T at position 189 and SEQ ID NO: 2 has a C at position 189. The specification provides GenBank accession numbers for several sequences corresponding to sequences obtained from bovines (p.34). However, while the specification provides reference to GenBank entries, neither the specification nor the sequence listing contain any information pertaining to the gene sequences other than SEQ ID NO: 1 and 2, identified as a T-allele or a C-allele. Reliance upon GenBank records does not provide an adequate written description for the claimed invention, as the content in a GenBank record can change over time as the records can be updated as time passes. In this case a potential update to the any cited GenBank record may result in a change in the nucleotide sequence associated with that GenBank accession number. Thus the reliance of an external GenBank sequence for a numbering scheme is similar to the recitation of a trademark, in that the GenBank accession number does not represent a fixed disclosure of a sequence, but instead refers to a record that is constantly able to be updated and modified. Similarly, reference to a nucleic acid sequence simply by a gene identifier such as 'ob' does not provide any structural limitations to the sequence analyzed in the claimed methods. The claims thus encompass a wide variety of distinct nucleic acid sequences which are broadly addressed as T-allele or C-allele of the ob gene.

In analyzing whether the written description requirement is met for genus claims,

it is first determined whether a representative number of species have been described by their complete structure. The instant specification provides only the sequences of SEQ ID NOs: 1 and 2 as the sequences of portions of the bovine ob gene containing a T or a C at position 189, respectively. The specification also provides the nucleotide sequences of SEQ ID NO: 4, 5, 6, and 7, asserted by the specification to be primers and probes specific for the ob gene (p.37), however it is unclear how these sequences are related to the sequences provided as SEQ ID NO: 1 and 2, or any other ob gene sequence. The specification provides no other ob gene sequences, nor any other polymorphic variants of any ob gene.

Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (e.g. other than nucleotide sequence or position within a particular gene), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case, while the specification asserts that any ob gene from any animal can be used (p.32), there is no guidance as to identify a T-allele or C-allele of an ob gene with the required functionality (i.e. indicative of a milk production), and in fact the specification provides no guidance as to how one may *a priori* identify either an ob gene or a polymorphism in an ob gene that is a T-allele or C-allele indicative of a phenotype.

Applicants' attention is directed to the decision in *In re Shokal*, 113 USPQ 283 (CCPA 1957) wherein is stated:

It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. *In re Soli*, 25 C.C.P.A. (Patents) 1309, 97 F.2d 623, 38 USPQ 189; *In re Wahlforss et al.*, 28 C.C.P.A. (Patents) 867, 117 F.2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will

vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, or perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

In the instant application, because the only structural information provided regarding polymorphic nucleic acid sequence variants related to milk productivity are the sequences of SEQ ID NO: 1 and 2, one of skill in the art cannot envision the detailed chemical structure of the nucleic acids encompassed by the claimed methods (i.e. an T-allele or C-allele of an ob gene), regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that such nucleic acids are part of the invention and reference to a potential method for identification. The particular nucleic acids are themselves required.

In conclusion, the limited information provided regarding the nucleic acids of the claimed methods is not deemed sufficient to reasonably convey to one skilled in the art that Applicant is in possession of a method for identifying animals with particular phenotypic traits based on the determination of gene polymorphisms or T-alleles and C-alleles of an ob gene, at the time the application was filed.

Thus, having considered the breadth of the claims and the provisions of the specification, it is concluded while the specification provides an adequate written description of:

Methods requiring the detection of a T-allele comprising SEQ ID NO: 1 or a C-allele comprising SEQ ID NO: 2,

The specification does not provide adequate written description for the claims as instantly presented.

Response to Remarks

Applicants have traversed the rejection of claims under 35 USC 112 1st ¶ for failure to adequately described the claimed invention. Applicants' arguments (p.9-10 of Remarks) have been fully and carefully considered but are not found to be persuasive.

Initially Applicants argue that the claims have been amended to be limited to bovines. It is noted that the portions of the rejection regarding non-bovine animals have been withdrawn from the rejection as set forth in this Office Action.

Applicants argue that the claims require the primers SEQ ID NO: 4 and 5 and the probes SEQ ID NO: 6 and 7, thus limiting the claims to a very specific portion of the bovine ob gene. The argument is not persuasive. Initially it is noted that only claims 1, 2, and 7 require the sequences as set forth in the aforementioned SEQ ID NOs. Furthermore, while applicants argue that the aforementioned SEQ ID NOs have homology to the sequence where the SNP resides, the Examiner maintains that sequence analysis of the SNP-containing sequences of SEQ ID NO: 1 and 2 and the primers SEQ ID NO: 4 and 5 and the probes SEQ ID NO: 6 and 7 do not reveal any homology between the required primers and probes and the SNP-containing sequences.

Applicants further argue (p.10 of Remarks) that SEQ ID NO: 1 and 2 are specific sequences generated from analysis of bovine DNA, and while a GenBank entry may change over time, the sequences as set forth in SEQ ID NO: 1 and 2 will not change. The argument is not found to be persuasive as none of the instant claims in fact require either of the sequences as set forth in either SEQ ID NO: 1 or 2.

The rejection as set forth is **MAINTAINED**.

Maintained Claim Rejections - 35 USC § 112 1st – Scope of Enablement

12. Claims 1, 2, 7-10, 12-18, and 22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A method for identifying a bovine having greater milk productivity comprising detecting at least one copy of SEQ ID NO: 1 in said bovine dairy cattle, and identifying the bovine dairy cattle having at least one copy of SEQ ID NO: 1 as an animal having greater milk productivity as compared to a bovine dairy cattle having two copies of SEQ ID NO: 2, wherein the greater milk productivity is an increased milk production during the first 200 days of lactation,

does not reasonably provide enablement for the detection of any other measure of milk productivity, by the detection of any other particular nucleotide content. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Nature of the invention and breadth of the claims

The claims are drawn to methods for the identification of animals with particular phenotypic traits based on the determination of nucleotide content at polymorphic positions in the ob (leptin) gene.

The claims encompass any measure of increased milk productivity.

The claims encompass the detection of any T-allele or C-allele of an ob gene.

The nature of the claims requires knowledge of the association of particular ob gene variants in animals and phenotypes related to milk productivity.

Direction provided by the specification and working example

The instant specification provides an analysis of the detection of SEQ ID NO: 1 and 2 (where SEQ ID NO: 1 has a T at position 189 and SEQ ID NO: 2 has a C at position 189) in bovine dairy cattle and the association of particular phenotypic traits in animals with either 1 or two copies of SEQ ID NO: 1 as compared to animals with two copies of SEQ ID NO: 2. The specification teaches (Table 3, p.70) that animals with either one or two copies of SEQ ID NO: 1 (the T containing allele) have a statistically significant increase in the amount of milk produced (as measured in kilograms/day) during the first 100 days and days 101-200 of lactation compared to animals having two copies of SEQ ID NO: 2 (the C containing allele).

The instant specification teaches that analysis of ob gene alleles was by a previously disclosed PCR-RFLP method (Example 1 - p.68). The specification does not provide any example in which particular polymorphisms of the ob gene are determined using SEQ ID NOs: 4, 5, 6, and 7.

The instant specification does not provide any analysis of any nucleotide sequences other than SEQ ID NOs: 1 and 2, nor any polymorphic positions other than position 189 of SEQ ID NOs: 1 and 2 where position 189 is either a T or a C.

State of the art, level of skill in the art, and level of unpredictability

While the state of the art and level of skill in the art with regard to the detection of any particular nucleic acid sequence, or the detection of a polymorphic variant in a particular sequence is high, the level of unpredictability with regard to associating the presence of a nucleic acid sequence or any particular polymorphic variation, to any

particular phenotype is even higher. The unpredictability is demonstrated by the prior art, the post filing art, and the instant specification.

Because the claims encompass the detection of polymorphisms in the ob gene using PCR amplification primers of SEQ ID NO: 4 and 5 and hybridization probes consisting essentially of SEQ ID NO: 6 and 7 it is relevant to point out that while the specification asserts that such nucleic acids (page 37-38) can be used for the analysis of the ob gene polymorphisms of SEQ ID NO: 1 and 2, the specification does not provide any example in which the aforementioned primers and probes are actually used in ob gene analysis. A search of the nucleotide sequences of SEQ ID NO: 4, 5, 6, and 7 does not indicate that these sequences are in any way related to the ob gene, or the particular T to C polymorphism of SEQ ID NO: 1 and 2. It is thus entirely unpredictable as to how one might use such sequences in an analysis of any ob gene.

Because the claims encompass any measure of milk productivity it is relevant to point out that the while the instant specification teaches that animals with one or two copies of the T-containing allele (SEQ ID NO: 1) have a statistically significant increase in the number of kilograms of milk produced per day during the first 200 days of lactation as compared to animals having two copies of the C-containing allele (SEQ ID NO: 2), there is not a statistically significant increase during the entire lactation, or during the time period of 200 days after the start of lactation (Table 3). It is thus unpredictable as to how one might identify an animal with greater milk productivity during an entire lactation by an analysis of ob gene polymorphisms.

Because the claims encompass a C to T transition that results in Arg25Cys it is relevant to point out that while the specification teaches a particular polymorphism (T to C at position 189 in SEQ ID NO: 1 to SEQ ID NO: 2) that causes a specific Arg to Cys change in an amino acid sequence encoded by SEQ ID NO: 1 and 2, the specification teaches, for example, that the bovine amino acid sequence can be the sequence from GenBank AAE82807 (p.33 of the specification). However, a sequence corresponding to GenBank AAE82807 contains neither a Cys or an Arg at position 25. It is thus entirely unpredictable as to whether or not a polymorphism that can be identified as 'a C to T transition that results in Arg25Cys' would in fact be indicative of a particular phenotype in the same was as the particular polymorphisms actually analyzed in the example of the instant specification.

Because the claims are drawn to the detection of the T-allele and C-allele of the ob gene, it is relevant to point out that while the specification teaches a particular T to C polymorphism (at position 189 in SEQ ID NO: 1 to SEQ ID NO: 2), there are other polymorphisms in the bovine ob gene, distinct from the polymorphism of the instant application, that can be considered T-alleles and C-alleles of the ob gene. For example, the post-filing art of Madeja et al (2004) teaches that there is an HphI polymorphism (a C/T substitution resulting in a change from valine to alanine) in exon 3 of the bovine gene (p.3925, right col., Ins.13-14), and addresses the genotype of animals as CC, CT, and TT in reference to this polymorphism (Table 2; p.3926, left col). It is thus unpredictable as to how the detection of an allele broadly described as, for example 'the

T-containing allele of the ob gene' would be used to identify an animal having any particular phenotypic trait.

Because the claims encompass methods wherein 'TT animals homozygous with respect to the T-allele of the ob gene have a greater milk productivity than CT animals heterozygous with respect to the T-allele' (claim 13) it is relevant to point out that the data presented in Example 1 (Table 3) compares only the TT genotype and TC genotype with the CC genotype, and there is in fact no indication of a statistically significant difference between milk production in TT animals as compared to CT animals.

The claims encompass methods of increasing milk production comprising increasing the amount of feed for a selected group of animals. The instant specification provides Example 3 (pages 73-78), which is a proposed analysis of leptin genotype associated with milk production and energy balance, but does not provide any results regarding any statistically significant association between genotype and feed conversion. Additionally, Example 4 (pages 78-82) is a study of the relationship between leptin genotype, milk production, milk compositions, and dry matter intake. However, Example 4 does not indicate whether or not there is any statistically significant correlation between any particular genotype and feed conversion efficiency as determined by, for instance, pounds of dry matter per kilograms of milk produced per day. Similarly, provisional application 60/509,755 provides no statistically significant correlation between leptin genotype and dry matter per pound gained in a study of 8 cattle (2 TT, 3 CT, and 3 CC), and provisional application 60/466,523 does not teach a

study in which feed conversion is analyzed in a controlled manner (e.g. the amount of dry matter consumed by any particular animal is recorded and related to genotype and carcass grade). Thus while the specification does not provide any statistically significant correlation between genotype and any measure of feed conversion efficiency, the prior art of Thisted (1998) provides guidance as to what is required to indicate that an association is statistically significant (Thisted teaches that it has become scientific convention to say that a P-value of 0.05 is considered significant (p.5 - What does it mean to be 'statistically significant'), and that values above the conventional reference point of 0.05 would not be considered strong enough for the basis of a conclusion). It is thus unpredictable as to whether or not one can reliably identify an animal with greater feed conversion efficiency based on ob gene polymorphism detection.

Quantity of experimentation required

A large and prohibitive amount of experimentation would have to be performed in order to make and use the claimed invention in the full scope of the claims. Such experimentation would require determining that particular ob polymorphisms are associated in a significant fashion with any measure of milk productivity (such as milk production over the entire lactation). Given the breadth of the claim language regarding the determined polymorphism (e.g. C-allele of the ob gene), one would also be required to analyze the nucleotide content at a large number of positions within any ob gene sequence to determine associations with milk production or feed conversion efficiency. One would also have to determine how the use of primers and probes of SEQ ID NO:

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4, 5, 6, and 7 would provide information regarding any ob gene polymorphisms related to milk production or feed conversion. Such experimentation would also include determining any association with any measure of milk production. The required experimentation would involve the analysis of an enormous number of polymorphic sequences, and large case:control studies in multiple populations.

Conclusion

Taking into consideration the factors outlined above, including the nature of the invention and breadth of the claims, the state of the art, the level of skill in the art and its high level of unpredictability, the lack of guidance by the applicant and the specific working example, it is the conclusion that an undue amount of experimentation would be required to make and use the claimed invention in the full scope of the claims.

Response to Remarks

Applicants have traversed the rejection of claims under 35 USC 112 1st ¶ for lack of enablement in the full scope of the claims. Applicants' arguments (p.10-12 of the Remarks) have been fully and carefully considered but are not found to be persuasive.

Initially Applicants argue that the claims have been restricted to bovines, and feed conversion efficiency has been deleted. It is noted that the portion of the rejection regarding analysis of non-bovine animals have been withdrawn from the rejection as set forth in this Office Action. With regard to feed conversion efficiency, it is noted that independent claim 16 still encompasses aspects of feed conversion as the claim requires "increasing the amount of feed" for a group of animal selected based on ob genotype.

Applicants argue that the specification contemplates the functional polymorphism as listed in position 189 of SEQ ID NO: 1 and 2, and that "the level of predictability that is significant at 95% is what is accepted by the scientific community". The arguments are not persuasive to overcome the rejection. As set forth in the rejection, none of the claims particularly require the specific sequences as set forth in SEQ ID NO: 1 and 2. While the specification may provide analyses of traits associated with the nucleotide content as set forth in SEQ ID NO: 1 and 2, the breadth of the claims is in no way limited to those sequences.

Applicants argue that while SEQ ID NO: 4-7 (as recited in claim 1) are not the sequences with the highest homology to SEQ ID NO: 1 and 2, they are nonetheless homologous to these SNP-containing regions. The argument is not persuasive. The Examiner has searched the sequences as set forth in SEQ ID NO: 4-7, as well as performed sequence analysis and comparison of SEQ ID NO: 407 and SEQ ID NO: 1 and 2 and found no homology between the sequences recited in the claims, and the sequences of the SNP-containing region of the ob gene as taught in the examples of the specification.

Applicants have argued that the instant specification teaches an association between the T-allele of the ob gene and quantity of milk produced in the 101-200 days in milk. This argument is persuasive. After review of the data of Table 3 the indicated enabled scope, as presented in this Office Action, has been broadened to include increased milk production during the first 200 days of lactation.

Applicants have further argued that Table 3 supports that a T-allele is indicative of increased milk production over the whole lactation. The argument is not found to be persuasive. While Table 3 includes data regarding the entire lactation of bovines, the data indicates that there is not a statistically significant (i.e. $p < 0.05$ is required for significance) increase in milk production in TC animals compared to CC animals (i.e. $p = 0.12$), and when the data for >200 DIM is analyzed as a separate component, Table 3 indicates no significant relationship between milk production and ob genotype. Furthermore, in this regard it is relevant to point out that the post-filing art of Chebel et al (2008), which indicates that the same polymorphism is not associated with milk yield at 305 DIM (i.e. $p = 0.2897$ – Table 3). It is noted that the reference of Chebel et al is cited only to support the Examiner's assertion and rebut Applicants' argument, and is not required for or added as part of the rejection.

Finally Applicants argue that it is possible to test if there is a significant difference between TT and TC animals with regard to milk production, but that no such test has been performed. This argument is not persuasive to consider the instant disclosure enabling in this regard. The specification lacks any statistically comparative analysis of the amount of milk produced in any TT versus TC animal. Thus it is unclear if, for example, in DIM 101-200, if the average of 1.74 kg/d of milk produced by a TT animal is significantly more than the 1.38 kg/d average produced by a TC animal. While applicants assert that the significance could be measured, there is no actual measurement. This is relevant given that, for example, in the 'Entire lactation' analysis a 0.91 average difference (i.e. TC versus CC) is not significant (i.e. $p = 0.12$), and there is

less of a difference (i.e. 0.36 kg/d different) between TT and TC animals at 101-200 DIM.

The rejection as set forth is **MAINTAINED**.

Maintained Claim Rejections - 35 USC § 102

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claims 8-10, 12, and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Konfortov et al (1999) as evidenced by GenBank GI: 4468136 (1999).

Konfortov et al teaches an analysis of polymorphic positions of the bovine ob (leptin) gene. The analysis includes the polymorphic 305 C/T position (Table 2) which is the polymorphism of position 189 of SEQ ID NO: 1 and 2 of the instant application, as evidenced by GenBank GI: 4468136.

Regarding claim 8, Konfortov et al teaches determining the genotype of animals within the leptin gene, which is the ob gene (p.1142 – Materials and methods). The reference teaches determining the genotype at the 305 C/T polymorphic position in the leptin gene, which is inherently associated with milk production, relevant to step (a). The reference teaches the grouping of genotyped animals in Figure 2, where CC animals are in a group with green squares in column four, TT animals are grouped with red squares in column four, and CT animals are grouped with blue squares in column

four. Thus animals with T-containing alleles are grouped with red and blue (not green) squares in column four.

Regarding claim 9, the TT and CT animals grouped with red and blue (not green) squares in column four (Fig 2) have genotypes that are inherently associated with increased milk production during the first 100 days of lactation.

Regarding claim 10, Konfortov et al teaches determining the genotype of animals within the leptin gene, which is the ob gene (p.1142 – Materials and methods). The reference teaches determining the genotype at the 305 C/T polymorphic position in the leptin gene including TT, CT, and CC genotypes.

Regarding claim 12, Konfortov et al teaches the identification of animals with T-containing alleles of the ob gene, where the allele possesses a T at position 305 of the leptin gene (as indicated in GenBank GI: 4468136), which is an allele that is inherently associated with increased milk production.

Regarding claim 13, Konfortov et al teaches group of animals that are homozygous TT for the ob gene genotype, as well as animals that are CT heterozygous for the ob gene genotype.

It is noted that this rejection of claims under 35 USC 102 cites multiple references. However, the additional reference (GenBank GI: 4468136) is cited as it provides evidence of the inherent characteristics of the method of Konfortov et al, specifically that the methods taught by Konfortov et al comprise analysis of a polymorphic variant of the ob (leptin) gene inherently associated with milk productivity (see MPEP 2131.01).

Response to Remarks

Applicants have traversed the rejection of claims under 35 USC 102 as anticipated by the prior art of Konfortov et al. Applicants' arguments (p.12-13 of Remarks) have been fully and carefully considered but are not found to be persuasive. Applicants argue that the cited reference does not contemplate a "method of increasing milk production". This argument is not found to be persuasive. It is noted that while the rejected claims include recitations of 'milk production' and 'milk productivity', the active process steps required by the claims merely require "determining their ob genotype" (claim 8 part (a), and claim 12) and "selecting animals" (claim 8 part (b)). The methods of the cited reference teach the same active process steps as the claimed methods. The intended use of the claimed method, as set forth in the preambles of the rejected claims, are not given patentable weight in the examination of the required structural limitations of the claimed kit in view of the prior art. As noted in the MPEP 211.02:

'a preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone'.

Further, in *Pitney Bowes Inc. v. Hewlett-Packard Co.*, 182F.3d 1298, 1305, 51 USPQ2d 1161, 1166 (Fed Cir. 1999) the court held that if the body of the claim sets forth the complete invention, and the preamble is not necessary to give "life, meaning and vitality" to the claim, 'then the preamble is of no significance to claim construction because it cannot be said to constitute or explain a claim limitation'.

Applicants further argue that the polymorphism analyzed in the cited reference, which is the same polymorphism disclosed in the instant specification, "is not inherently associated with milk production traits". However this statement is incongruous with the other arguments of the Remarks that Applicants have provided in the traversal of the rejection of claims under 35 USC 112 1st ¶. Applicants have argued that "because genomics are indeed predictive of biological systems behavior, once an association has been established between an allele (i.e. T allele) and milk production it allows one to a priori identify the genotype.....and be indicative of the phenotype". While Applicants may have performed some statistical analysis to show a particular association exists, if a genotype:phenotype association exists then that association must be an inherent property of the asserted genotype (i.e. prior to any analysis by Applicants, the asserted association, if true after the analysis, would have been true prior to the analysis).

The rejection as set forth is **MAINTAINED**.

Conclusion

15. No claim is allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Kapushoc whose telephone number is 571-272-3312. The examiner can normally be reached on Monday through Friday, from 8am until 5pm.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Stephen Kapushoc/
Art Unit 1634

/Jehanne S Sitton/

Primary Examiner, Art Unit 1634